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COVID-19 Rapid Letter

Role of neoadjuvant radiochemotherapy for esophageal cancers over pre/peri-operative chemotherapy in the era of COVID-19 and beyond[☆]

Dear Editor, we read with interest the paper of Tchelebi et al. addressing the choices for optimizing clinical indication and resources along the current pandemic scenario [1]. In regard of locally advanced esophageal cancer they suggest to apply preoperative concurrent radiochemotherapy (pRTCT), being the standard option; it should be given using the shortest fractionation scheme possible. Finally, induction chemotherapy is mentioned as alternative to delay the initiation of daily radiotherapy, but that statement, although in view of subsequent RTCT, was controversial among authors due to still non mature supporting data. We agree with Authors, since we believe RTCT is standard for esophageal cancers. Of note, esophagogastric junctional (EGJ) anatomic sub-sites as described by Siewert classification [2] belong to esophageal cancers for Siewert I and II, while type III belong to gastric primary, as by current TNM classification [3]. Actually two of the most representative international Guidelines report this indication [4–7]. NCCN guidelines also include preoperative chemotherapy (pCT) as an option for esophageal cancer, but specify that pRTCT is the preferable option. In this perspective also along Covid scenario pRTCT should remain the best option. Conversely, ESMO guidelines include pRTCT and pCT at the same priority level: in this perspective avoiding daily access to hospital for pRTCT favoring a cyclic access for pCT could be maybe preferable. We do believe that the NCCN indication is the most embraceable. Efficacy and safety of pRTCT have been unequivocally demonstrated by randomized controlled trials (RTrials) [8,9], with long-term follow-up [10], for both squamous (SCC) and adenocarcinoma (ADK) histology [9,10], gaining significant improvement of overall survival and local control [11]. Sometimes in scientific research and current clinical practice (e.g.: multidisciplinary tumor board) pCT is advocated as superior of preferable to pRTCT at least for adenocarcinoma histology and/or for Siewert type II junctional presentations. That is usually on the basis of Guideline indications such as ESMO [5] and on the efficacy reported for ADK (often derived by RTrials on gastric primaries [12,13] or by efficient pCT schedules as FLOT, not tested over pRTCT in RTrials [14]. Current evidence based superiority of pRTCT over pCT also for ADK is supported by some arguments. First: the mentioned evidences by trials specifically signif-

icant for ADK [9,10]; then, the evidence base supporting pRTCT derive from RTrials in esophageal cancer, while that is not always the case for pCT [12]. Notably, CROSS trial accrued 25% of EGJ, 57.5% of distal localization and 75% of ADK [9]. Sjoquist et al. in a meta-analysis on 24 studies (accounting for 4188 patients) reported survival benefit of pRTCT or pCT over surgery alone in patients with esophageal carcinoma [15]. Although Authors didn't found clear advantage of pRTCT over pCT, they reported that the hazard ratio (HR) for all-cause mortality with pRTCT was 0.78 (95% CI 0.70–0.88; $p < 0.0001$), significant for both histologies in subgroup analyses; while HR of pCT was 0.87 (0.79–0.96; $p = 0.005$), only significant for ADK. In summary both pRTCT and pCT are significantly effective for esophageal cancer, but with much different magnitude, favoring pRTCT. Finally Ronellenfitsch et al. published a meta-analysis on 14 studies (accounting for 2422 patients) only focused on ADK (esophageal, gastric and EGJ) [16]. In their analysis neoadjuvant (CT-based, including radiotherapy) approach significantly improved clinical outcomes over surgery-only. In subgroup analysis they found higher efficacy in EGJ and for pRTCT compared to pCT, but the tests for subgroup differences were not statistically significant due to the low number of patients enrolled in direct comparison trials. These evidences influenced the position of NCCN. In conclusion we do believe that pRTCT should be preferred to pCT both in Covid era and beyond, currently being the gold standard for both SCC and ADK (including Siewert type I and II). An open issue could be superiority of pCT for non-EGJ (upper, middle and lower third) presentations. Thus Guidelines should consider this issue and specifically address it.

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